m(6)A RNA modification controls cell fate transition in mammalian embryonic stem cells.

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Public Summary:
This work shows that a chemical tag on RNAs, called m6A, is particularly important for embryonic stem cells to control their cell fates. m6A is placed on RNAs that encode important stem cell factors; the presence of this tag ensures that the stem cells can remove those RNAs when the time is right. Thus, stem cells have a specialized mechanism to help them turn on a dime, changing from one kind of cell into another.

Scientific Abstract:
N6-methyl-adenosine (m(6)A) is the most abundant modification on messenger RNAs and is linked to human diseases, but its functions in mammalian development are poorly understood. Here we reveal the evolutionary conservation and function of m(6)A by mapping the m(6)A methylome in mouse and human embryonic stem cells. Thousands of messenger and long noncoding RNAs show conserved m(6)A modification, including transcripts encoding core pluripotency transcription factors. m(6)A is enriched over 3' untranslated regions at defined sequence motifs and marks unstable transcripts, including transcripts turned over upon differentiation. Genetic inactivation or depletion of mouse and human Mettl3, one of the m(6)A methylases, led to m(6)A erasure on select target genes, prolonged Nanog expression upon differentiation, and impaired ESC exit from self-renewal toward differentiation into several lineages in vitro and in vivo. Thus, m(6)A is a mark of transcriptome flexibility required for stem cells to differentiate to specific lineages.